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PATENT
Attorney Docket No. **HOGAN-04448**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Kirk Hogan		
Serial No.:	09/613,887	Group No.:	1655
Filed:	07/11/01	Examiner:	J.E. Goldberg
Entitled:	Methods and Compositions for Perioperative Genomic Profiling		

AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION DATED OCTOBER 24, 2001

Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 C.F.R. 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being sent by facsimile transmission to the U.S. Patent and Trademark Office, via Examiner J.E. Goldberg at (703) 746-5149.

Dated: 2-8-02 By: Mary Ellen Waite
Mary Ellen Waite

Madam:

The following communication is responsive to the Office Action mailed October 24, 2001, due on or before January 24, 2002. A request for a one-month extension of time to extend the time of response from January 24, 2002 to February 24, 2002 is attached. The Applicant respectfully requests reconsideration of the Application in view of the following amendment and remarks.

A clean version of the rewritten, added, and/or cancelled claims with instructions for entry pursuant to 37 C.F.R., Section 1.121(c)(1)(i) is included beginning on the next page of this communication. A marked-up version of the rewritten, added, and/or cancelled claims pursuant to 37 C.F.R., Section 1.121(c)(1)(ii) is attached as Appendix I. A clean version of the entire set of pending claims pursuant to 37 C.F.R., Section 1.121(c)(3) as they should appear following entry of this amendment is attached as Appendix II.

I. **IN THE CLAIMS:**

Please substitute the following claims for the previously pending claims.

Sub D1

C1

21. A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure associated with known genetic variations comprising:

a) obtaining a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure; and

b) subjecting said sample to an assay for detecting two or more genetic markers to generate a genomic profile for use in selecting a perioperative course of action, wherein said subjecting step occurs after said patient is scheduled for surgery but before completion of said surgical procedure, thereby determining a risk for complications during said surgical procedure.

Sub D3

C2

32. A method for selecting conditions for a surgical procedure by screening a patient perioperatively to determine a risk for complications during a surgical procedure associated with known genetic variations comprising:

a) providing a sample from a perioperative subject; and

b) subjecting said sample to an assay for detecting two or more genetic markers known to be associated with perioperative phenotypes to generate a genomic profile for use in selecting a surgical procedure treatment course of action; and

c) subjecting said subject to a surgical procedure, wherein conditions for said procedure are selected using said genomic profile.

Sub D4

C3

37. A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure from known genetic variations comprising:

a) obtaining a sample from a perioperative subject; and

b) subjecting said sample to an assay for detecting two or more genetic markers clinically associated with two or more conditions selected from the group consisting of butyrylcholinesterase deficiency, poor debrisoquine metabolism, thrombus, and malignant hyperthermia to generate a genomic profile, wherein said genomic profile provides information for use by a physician in determining a risk for complications during a surgical procedure.

REMARKS

Claims 1-20 were filed in the original case. Claims 1-20 were cancelled and Claims 21-41 were added in a previous amendment. Therefore Claims 21-41 are currently pending.

In the Office Action dated October 24, 2001, the Examiner has withdrawn rejections from the previous Office Action. However the Examiner added a number of new rejections. The currently pending rejections are:

1) Claims 21-41 stand rejected under 35 U.S.C. 112, second paragraph;
2) Claims 21 and 24 stand rejected under 35 U.S.C. 102; and
3) Claims 21-41 stand rejected under 35 U.S.C. 103.

Each of these grounds of rejection is addressed in detail below. Applicant thanks the Examiner for the phone interview conducted on February 5, 2002, which has resolved many of the issues discussed below.

1) The Claims are Definite

The Examiner has rejected the claims as being allegedly indefinite. Applicant must respectfully disagree. Each of the Examiner's rejections are addressed in turn.

A. "Known"

The Examiner has argued that the term "known" is indefinite because the term is not defined and it is allegedly unclear what time frame the term includes (e.g., at time of filing, time of publication, time of reading). Applicant respectfully disagrees. The specification provides explicit support for the term "known." For example:

"The sequence of the markers should be known. In preferred embodiments, the markers are mutations in a given gene known to have an associated phenotype. Large amounts of sequence data and known mutations or polymorphisms are known and accessible." Page 26 paragraph starting at line 9.

"Markers for inclusion in perioperative genomic profiles are selected based on specific criteria. The sequence of the mutation or polymorphism, as well as the clinical outcome of carrying a mutant allele, should be known." Page 25, last full paragraph.

"In some embodiments of the present invention, the genetic markers are single nucleotide polymorphisms ("SNPs"). Known SNPs are available from public and private databases (see above)." Page 26, first sentence under section A.
"Markers that are predictive of BChE deficiencies are known (*See e.g.*, La Du *et al.*, Cell. and Molec. Neurobiol., 11:79 [1991])." Page 30, last paragraph.

There are numerous other descriptive uses of the term "known" in the specification. One skilled in the art, upon reading the specification and claims, would understand that the term "known" refers to genetic variations that are known at the time that the claimed method is being carried out. In view of the above, Applicant requests that the rejection be withdrawn.

B. "before completion of said surgery"

The Examiner has argued that the phrase "before completion of said surgery" is unclear. Applicant respectfully disagrees and asserts that the ordinary meanings of the terms apply and are clear. However, in order to further the prosecution of the present case, while not acquiescing to the Examiner's argument, and retaining the right to prosecute the original claims (or similar claims) in the future, Applicant has amended the phrase to recite "before completion of said surgical procedure." In view of the above, Applicant requests that the rejection be withdrawn.

C. "perioperative subject"

The Examiner has argued that the term perioperative subject is not clear. Applicant respectfully disagrees. However, in order to further the prosecution of the present case, while not acquiescing to the Examiner's argument, and retaining the right to prosecute the original claims (or similar claims) in the future, Applicant has amended the claim. As amended the claims recites that the perioperative subject is "a patient scheduled for a surgical procedure

that has not yet completed said surgical procedure." In view of the above, Applicant requests that the rejection be withdrawn.

D.-F. Positive process steps

The Examiner argues that Claim 21 does not recite a positive process step relating back to the preamble. Applicant respectfully disagrees. However, in order to further the prosecution of the present case, while not acquiescing to the Examiner's argument, and retaining the right to prosecute the original claims (or similar claims) in the future, Applicant has amended Claim 21 to conclude with the phrase "thereby determining a risk for complications during said surgical procedure" which tracks language from the preamble. Claims 32 and 37 have been similarly amended for consistency.

The Examiner argues that Claim 32 does not recite a positive process step relating back to the preamble. Applicant respectfully disagrees. The final step of the claim recites the step of "subjecting said subject to a surgical procedure, wherein conditions for said procedure are selected using said genomic profile." Therefore the final step does recite a positive process step that relates to the preamble, since the final step carries out the action of a surgical procedure using conditions selected from the screening.

The Examiner argues that Claim 37 does not recite a positive process step relating back to the preamble. Applicant respectfully disagrees. However, in order to further the prosecution of the present case, while not acquiescing to the Examiner's argument, and retaining the right to prosecute the original claims (or similar claims) in the future, Applicant has amended the claim to recite the final step "wherein said genomic profile provides information for use by a physician in determining a risk for complications during a surgical procedure." This directly tracks the language of the preamble "a method of screening a patient perioperatively to determine a risk for complications during a surgical procedure from known genetic variations."

In view of the above, Applicant requests that these rejections be withdrawn.

2) The Claims are Novel

The Examiner has rejected Claims 21 and 24 as allegedly being anticipated by Connors et al. (hereinafter "Connors"). Applicant respectfully disagrees. Connors does not

teach all of the elements of the claims. For example, Connors does not teach obtaining a sample from a perioperative subject and assaying the sample after the period of surgery scheduling, but prior to completion of the surgical procedure. The Examiner argues that Connors teaches that the samples were tested prior to and following surgery. The Examiner does not show, nor does Connors teach, that the testing occur between the period of surgery scheduling, but prior to completion of the surgical procedure. Furthermore, the claim requires that the assay detect two or more genetic markers to generate a genomic profile for use in selecting a perioperative course of action. Connors does not teach assaying for two or more markers and does not teach assaying for markers useful in selecting a perioperative course of action (i.e., Connors does not teach or suggest a utility for the assay data in selecting a perioperative course of action). In view of the failure of Connors to teach all the elements of the claims, Applicant requests that the rejection be withdrawn.

3) The Claims are Non-Obvious

The Examiner has rejected the claims as allegedly being obvious in view of a number of references. None of these references, alone or in combination, teach or suggest genetic profiling in the perioperative period.

The cited references each teach detection of mutation. However, the Examiner concedes, in each rejection, that the samples are not tested in the perioperative period. This is correct, as none of the cited references teach that samples are tested in the perioperative period. During a phone interview conducted February 5, 2002, the Examiner stated that the Quane et al. (hereinafter "Quane") reference is the closest cited prior art. Quane fails to teach or suggest the presently claimed invention for a number of reasons.

For example, Quane, like the other cited references, fails to teach that samples are tested in the perioperative period. The Examiner points to language on page 141, column 2 of Quane where the reference states "Once an individual is diagnosed as being susceptible to MH, the anaesthetics which trigger this syndrome can be avoided." However, this language does not teach testing in the perioperative period. In Quane, subjects were tested following a poor reaction to an anesthetic during surgery. These post-surgical subjects were tested to identify a polymorphism. In contrast to the presently

claimed invention, these subjects were not tested in the perioperative period, nor would these patients be tested in the perioperative period for any future surgery as they have already been characterized. Therefore, there is no teaching in Quane to conduct perioperative testing. Quane does not teach or suggest that everyone (e.g., people who are generally believed to be healthy going into the test) should be screened prior to surgery.

From the interview with the Examiner, it was made clear that Quane is being used in the rejection to suggest that genetic polymorphisms could find use for testing in the perioperative period and therefore, medical practitioners would seek to test people in the perioperative period to identify people that might have a polymorphism that would lead to a bad outcome from surgery. This argument assumes that medical practitioners, using only the teachings of the prior art, would be motivated to test people in order to determine genetic risk for surgical complications. Applicant believes that the only teaching of such an application comes for the present invention and not from any prior art references. Indeed, based on the factual evidence provided below, it is clear that even if medical practitioners were aware of the Quane reference, they would not be motivated by the teachings of Quane (or any other reference) to undertake perioperative testing.

Prior to discussing such matters, Applicant further points out that Claim 37 states that two or more markers are tested corresponding to two or more conditions—i.e., phenotypes. The Quane reference only relates to a single phenotype. Even if medical practitioners decided to use the Quane information to test perioperatively (for the reasons discussed below—they would not), this does not lead the medical practitioner to test two or more markers for different conditions. To meet this element, the Examiner would have to identify prior art suggesting that medical practitioners would look at multiple markers in the perioperative period directed to two or more phenotypes. As discussed below, such testing is contrary to the practices of medical practitioners (and thus is non-obvious).

A) The evidence directly refutes the Examiner's position

All evidence in the record directly refutes the Examiner's position. Indeed, the state of the art teaches that testing for multiple markers (or single markers) in the

perioperative period should not be done. If, as the Office Action states, it would have been obvious to use the known markers of the prior art to reduce surgical risks, it is surprising that there are no examples of such use, considering that many markers have been known for many years, and suitable detection technologies have been available. The failure of medical practitioners to carry out such methods is evidence of the non-obviousness of the present invention. It is not surprising that medical practitioners have not used the prior art markers for perioperative testing. As described below, such testing is foreign to the perioperative medical field, which, even today, teaches that it should not be carried out. Further, as shown below, even when made aware of the present invention, skilled artisans do not believe that genetic testing should be carried out in the perioperative period.

Applicant submits herewith a Declaration of Kirk Hogan, M.D. The Declaration explains that, even today in February 2002 (let alone at the filing date of the present invention), the state of the art in medical practice is to not test subjects for multiple genetic markers in the perioperative period. Dr. Hogan explains facts that show, in view of the state of the art, one skilled in the art would not, upon reading the prior art references cited by the Examiner, recognize a benefit of testing individuals in the perioperative period and would not have been motivated to test these individuals in the perioperative period for the expected benefit of determining whether the patient possessed any mutation which were linked to known conditions. For example, a grant application entitled "Perioperative Genomic Profiles" submitted by Dr. Hogan to the Anesthesia Patient Safety Foundation (APSF), describing the subject matter of the present invention, was rejected by a panel of experts in the field on 11/27/2000 (i.e. after the filing date of the present disclosure 7/11/2000) because the state of the art teaches that such methods should not be carried out. The Grant Committee, composed of pre-eminent experts concerned with patient safety in the perioperative period, stated in full:

> "The APSF committee members reviewing your proposal to study genomic profiles were impressed by the elegance of the proposal. It would take the issue of patient safety in a new direction. It could improve the safety of the anesthetic experience, particularly for those patients with unknown diseases.
>
> The committee's concern and reason for not funding the study rested on a few factors. It is a basic science study without clear clinical value. In the value

equation the committee members considered the study might improve quality but the cost could be very high. As anesthesia practice has moved toward determining the ratio of quality to cost, this study seems to be *going in the opposite direction*. It suggests we screen everyone in the hopes we find something on almost everyone. *The direction of anesthetic evaluation is presently to not routinely do any preoperative studies.*

The committee members were also concerned that patient confidentiality and ethics are problematic. Do patients want to know all that is potentially wrong with them? The committee members were concerned that the findings of the study could well increase costs with little benefit to the patient." (emphasis added)

When presented with the subject matter of the present invention (not just a number of disparate papers describing markers and their correlations to phenotypes), the experts in the field of safety in the perioperative interval rejected the methods. They stated that the methods were in the "opposite direction" of the field and doubted the clinical value of such testing. They conclude by explaining the state of the art as: "The direction of anesthetic evaluation is presently to not routinely do any preoperative studies." Thus, the subject matter of the present invention is in direct contrast to ("going in the opposite direction" of) the teachings of the prior art. Medical practitioners would not, as the Examiner guessed, "clearly recognize the benefit of testing an individual prior to surgery" or "have been motivated to test these individuals prior to surgery for the expected benefit of determining whether the patient possessed any mutation which were linked to the known condition." Even if presented with the Quane reference (there is no reason to believe they would consult such work outside their review of the grant related to the subject matter of the present invention), these experts in the field would not have been led to conduct perioperative testing for the marker taught in Quane, let alone a plurality of markers. Indeed, the very grant application that the reviewers denied described RYR1 mutations disclosed in publications by Quane, including the reference cited by the Examiner.

As explained in the Hogan Declaration, the current state of the art is that medical practitioners try to minimize or avoid perioperative testing. In particular, testing of individuals, without a prior suspicion of a defect, is to be avoided (and therefore, one would not use a panel directed to a plurality of genetic markers, where some or most of the markers may be irrelevant for any particular subject). For example, a number of

modern book chapters and reviews, published after the filing date of the present application, demonstrate this understanding in the art with respect to biochemical testing (even these modern articles do not discuss genetic testing). The 2002 Pediatric Anesthesia text by Gregory (attached) states that routine perioperative testing (biochemical tests) in healthy infants and children should be avoided. The 2002 Clinical Anesthesia Practice text by Kirby et al. (attached) states that routine testing for healthy individuals in unnecessary.

A review article by Hopkins (attached) cites the Quane reference (page 125, footnote 108) and goes on to explain that the complexity of the molecular genetics of MH precludes DNA-based diagnosis at present. Thus, a modern analysis of the molecular genetics of MH (incorporating Quane and similar works) concludes that DNA-based testing for MH is precluded and not desirable. Therefore, in addition to the reasons stated above, an anesthesiologist, surgeon, or other perioperative caregiver, presented with the teachings of Quane and Hopkins, would not believe that perioperative genetic testing for MH polymorphisms would be useful.

B) The rejection is based on improper unsupported statements

While all of the factual evidence in the record demonstrates that one skilled in the art would not be instructed to carry out genetic analysis of two or more markers in the perioperative period, no such evidence is necessary to overcome the present rejection. Even if none of the evidence presented above had been submitted, the rejection would have to be withdrawn. The current obviousness rejection is based on a guess as to how skilled artisans would be instructed by the teachings of Quane and other references. The Office Action admits that the cited prior art references do not teach testing in the prior art period. To support the rejection, the Office Action argues that, while the teaching is lacking, one skilled in the art would make the leap and carry out perioperative genetic testing. This is an improper extension of the prior art teachings. The Federal Circuit has made it clear in a number of recent cases that such rejections are improper—and without more, cannot support a *prima facie* case of obviousness.

The Federal Circuit dealt with similar issues in the recent case *In Re Zurko* (decided August 2, 2001):

> "The Board said that communication along a trusted path, if not explicit in the prior art, is either inherent or implicit. Id. at 7. The Board further adopted the Examiner's assertion that 'it is basic knowledge that communication in trusted environments is performed over trusted paths.' Id. at 8. As for the motivation to combine these references, the Board concluded that it 'would have been nothing more then good common sense' to combine the teachings of these references. Id. . . . [T]he deficiencies of the cited references cannot be remedied by the Board's general conclusions about what is 'basic knowledge' or 'common sense' to one of ordinary skill in the art. . . This assessment of basic knowledge and common sense was not based on any evidence in the record, and, therefore, lacks substantial evidence support. . . . With respect to core factual findings in a determination of patentability . . .the Board cannot simply reach conclusions based on its own understanding or experience—or on its assessment of what would be basic knowledge or common sense. Rather, the Board must point to some concrete evidence in the record in support of these findings."

The Zurko case is similar to the present one. Here, the rejection relies on unsupported assertions to suggest that one skilled in the art would test samples in a perioperative period even thought the prior art provides no such teaching (as described above the art teaches away).

The Federal Circuit made a similar point in *In Re Dembiczak* (decided April 28, 1999). The court stated that a showing of obviousness must be "clear and particular . . . Broad conclusory statements regarding the teachings of multiple references, standing alone, are not 'evidence.'"

For the Examiner to support the present obviousness rejection, the Examiner must provide actual evidence showing that testing should occur in the perioperative period. Without such a showing (e.g., in the form of a reference, affidavit, or other concrete evidence—not in the form of an argument) the rejection must be withdrawn. For the reasons described above, Applicant believes such evidence does not exist—only evidence to the contrary exists, as described above. Applicant therefore requests that the rejection be withdrawn.

CONCLUSION

All grounds of rejection of the Office Action of October 24, 2001 have been addressed and reconsideration of the application is respectfully requested. It is respectfully submitted that Applicant's claims as amended should be passed into allowance. Should the Examiner

believe that a telephone interview would aid in the prosecution of this application Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: 2/8/02

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